

Pregnancy outcome in non-supplemented luteal phases

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Introduction

- What kind of pregnancy?
- If supplemented, how to supplement?
- How long to supplement?
- LPS for preventing a miscarriage?

A Pregnancy can be achieved after:

- Natural cycle
- CC/aromatase inhibitors stimulated cycles
- HMG/rec-FSH
 - With GnRH agonist
 - With GnRH antagonist

Luteal Phase defect in Natural cycle:

- As early as 1949, the premature onset of menses was recognized as indicative of a luteal phase deficiency of progesterone production, which was shown to be correctable by exogenous progesterone administration (Jones, 1979).
- The prevalence of a luteal phase defect in natural cycles in normo-ovulatory patients with primary or secondary infertility was demonstrated to be about **8.1%** (Rosenberg et al., 1980).

Causes of Luteal Phase defect in Natural cycle:

- disordered folliculogenesis
- defective corpus luteum function
- abnormal luteal rescue by the early pregnancy.
- A variety of clinical conditions, such as
 - hyperprolactinemia
 - hyperandrogenic states
 - weight loss
 - Stress
 - athletic training may result not in oligo- or anovulation, but rather may be manifest as LPD (Ginsburg, 1992).

How to define a luteal phase defect?

- Diagnosis remains controversial (Jordan et al., 1994)
- Defective luteal phase in natural cycle was defined if the serum mid-luteal progesterone levels are less than 10ng/ml (Jordan et al., 1994)
- Mid luteal P levels do not always reflect the endometrial maturation (Batista et al., 1994)
- The most reasonable consensus of a defective luteal phase is a lag of more than two days in endometrial histological development compared to the expected day of the cycle (Jones, 1991, Dawood, 1994).

CC-stimulated cycles

- Luteal phase inadequacy has been described in association with many drug regimens employed to stimulate the ovaries
- Some authors reported luteal phase inadequacy in up to 50% of clomiphene citrate induced cycles in anovulatory women and the administration of hCG to induce final oocyte maturation in these patients was not beneficial [Cook *et al.*, 1984, Keenan *et al.*, 1989].

CC-stimulated cycles

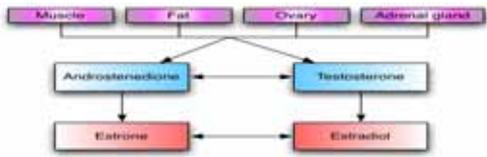
- CC occupies the hypothalamic estrogen receptors for several weeks (Dickey *et al.*, 1996)
- The long term receptor occupancy might lead to higher luteal LH concentrations (Van steirteghem *et al.*, 1988 and Tavaniotou *et al.*, 2003)
- In a pilot study, we could not show any difference in outcome between non supplemented CC/AI cycles with natural cycles (Fatemi *et al.*, 2003).

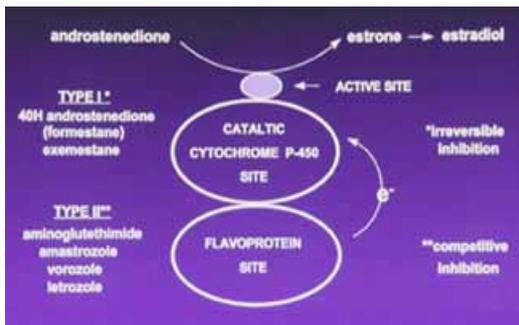
CC-stimulated cycles

However, no randomized controlled trials analysing the potential benefits of luteal phase supplementation in clomiphene citrate-stimulated cycles have yet been published.

Aromatase inhibitors stimulated cycles

Aromatase inhibitors prevent the action of cytochrome P450 or aromatase which catalyses the terminal step in the conversion of androgen to estrogen (Fatemi et al., 2002).







Any need for LPS?

- Again no RCT present
- However, in a pilot study, we could not show any difference in outcome between non supplemented CC/AI cycles with natural cycles (Fatemi et al., 2003).

HMG/rec-FSH stimulated cycles

- In order to increase the chance of obtaining embryos of suitable quality for transfer, ovarian stimulation was introduced.
- Ovarian stimulation results in multifollicular development
- Problem: the premature occurrence of LH.
 - One in five women stimulated with gonadotropin treatment could not reach oocyte retrieval due to an unpredicted rise of LH (Loumaye, 1990) causing ovulation before oocyte retrieval (Lejeune et al. 1986)

Solution:

- Suppression of the hypothalamic-pituitary-gonadal axis by peptides that act at the GnRH receptor (Struthers et al., 2007)
- Two types of GnRH analogues were available by the mid 1980s: GnRH agonists (Clayton and Catt, 1980) and GnRH antagonists (Karten and Rivier, 1986)
- Following discontinuation of GnRH agonist, pituitary responsiveness was not readily available, complicating the already disturbed luteal phase in IVF cycles (Smitz et al., 1992)

GnRH antagonists

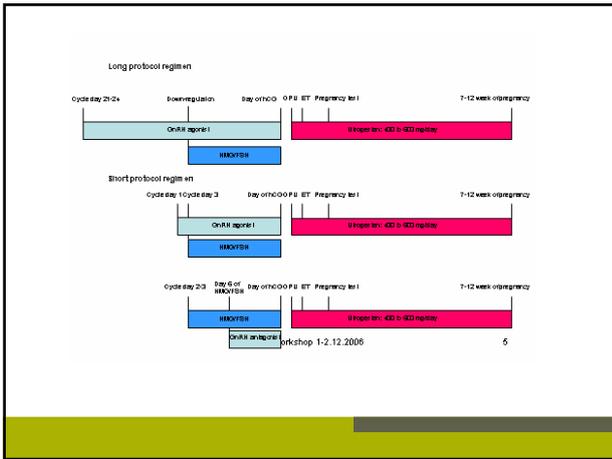
- GnRH antagonists act within a few hours after their administration with a rapid recovery of the pituitary within a few hours (Fatemi et al., 2002)
- Would the rapid recovery of the pituitary function (Albano et al., 1996) obviate the need for luteal phase supplementation? (Elter and Nelson, 2001)

LPS with GnRH-antagonist?

- Preliminary observations in intrauterine insemination (IUI) cycles seemed to favor the non supplemented GnRH antagonist cycles. (Ragni et al., 2001)
- Beckers et al. (2003), evaluated the non-supplemented luteal phase characteristics in patients undergoing ovarian stimulation with recombinant FSH combined with a GnRH antagonist.
 - unacceptably low pregnancy rates (overall 7.5%)
 - cancellation of the study after 40 patients were included.

LPS with GnRH-antagonist?

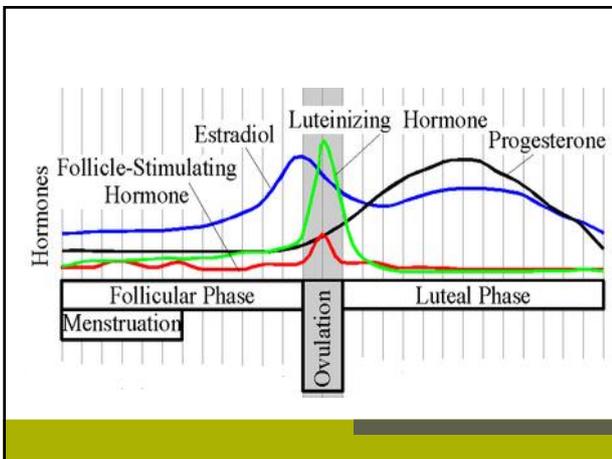
Despite the rapid recovery of the pituitary function in GnRH antagonist protocols (Dal Prato and Borini, 2005), luteal phase supplementation remains mandatory (Tarlantzis et al., 2006).



Luteal phase in natural cycle

Which hormones seem to be crucial during the luteal phase in a natural cycle?

- ✓ Progesterone
- ✓ Estradiol
- ✓ LH

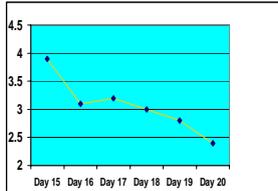


Role of progesterone

- Induces secretory transformation of the endometrium in the luteal phase (Bourgain *et al.* (1990).
- Progesterone deficiency delays endometrial maturation (Dallenbach-Hellweg G, 1984).
- Removal of CL prior to 7 weeks of gestation leads to pregnancy loss (Csapo *et al.*, 1972).
- Normal pregnancy was sustained when progesterone was given after removal CL (Csapo *et al.*, 1973)

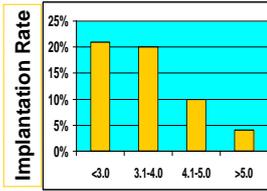
Role of progesterone

(De Ziegler *et al.*, 1996)



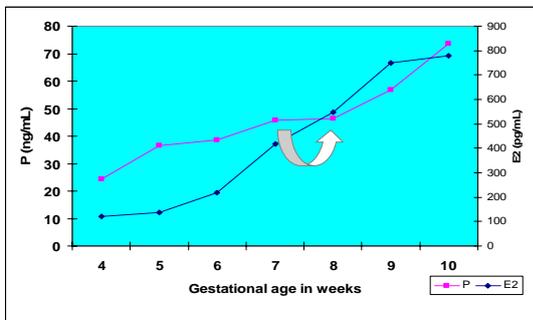
UC Frequency /Min

(Fanchin *et al.*, 1998)



UC/Min

Lutealplacental Shift



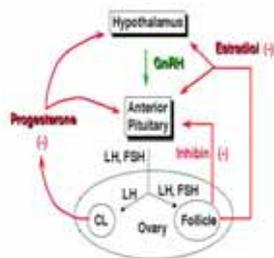
(Scott *et al.*, 1991)

Causes of luteal phase defect

- What is Aetiology of the luteal phase defect in stimulated cycles?
 - Oocyte retrieval?
 - GnRH agonist?
 - hCG?
 - Combination of those factors?

Luteal phase in ART cycles

- Iatrogenic luteal phase defect due to supraphysiological steroid levels in stimulated cycles
(Fauser and Macklon 2002)



Luteal phase support in ART

- a large number of trials has been conducted on LPS
- different formulations, doses, durations and routes of administrations are currently used

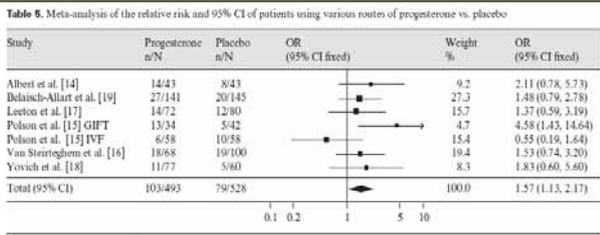
1. Means of LPS

- Progesterone -vaginal, intramuscular, oral
- Progesterone + E2
- hCG
- (GnRH agonist)

2. Onset of LPS

3. Duration of LPS

The use of progesteron in IVF



Test for heterogeneity: $\chi^2 = 7.35$, d.f. = 6, $p = 0.29$.
 Test for overall effect: $z = 2.70$, $p = 0.007$.

Nosarka et al., 2005

Progesterone in LPS



IM Progesterone

- Effective
- Physiological serum levels
- Painful (long, thick needles)
- Occasional sterile abscess
- Occasional allergic reaction (oil vehicle)
- Needs to be administered by nurse, husband
- Acute eosinophilic pneumonia associated with IM administration of progesterone as luteal phase support after IVF: 3 case report

IM Progesterone

- ✓ Vaginal and intramuscular progesterone had comparable implantation and clinical PRs (Penzias, 2002, Nosarka, 2005). (n=1675 cycles)
- ✓ Levin et al., 2000 in a multicenter U.S. study involving almost 2,000 women, found that, pregnancy rates were comparable between women who had used i.m. progesterone and those who had used vaginal gel

IM Progesterone

- Five studies (891 patients) compared the best route for progesterone administration: i.m. or vaginal (Artini et al., 1995; Perino et al., 1997; Abate et al., 1999; Anserini et al., 2001; Guesa et al., 2001)
- CPR and DR were significantly improved when i.m. progesterone was used, with combined RR of 1.33 (95% CI 1.02–1.75) and 2.06 (95% CI 1.48–2.88) respectively (Pritts et al., 2002)

IM Progesterone

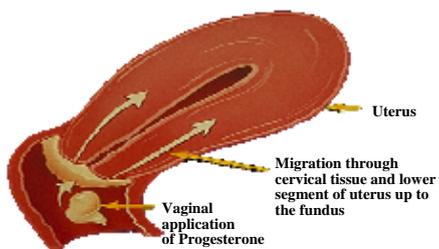
- The meta-analysis of Nosarka differed from Pritts and Atwood's in that this literature search covered a 20-year study period while Pritts and Atwood study period was only 7 years.
- Vaginal and intra muscular progesterone had comparable implantation and clinical PRs and DR (Nosarka et al.,2005)

Vaginal progesterone

- Effective
- Convenient (self-administration)
- First uterine pass effect /targeted delivery
- Might require multiple dosing /day (suppositories)

Vaginal progesterone

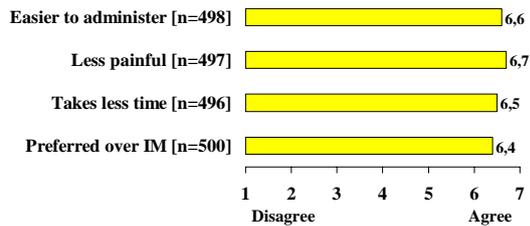
First uterine pass effect /targeted delivery



Vaginal progesterone

- High uterine concentration of progesterone
- Minimizes the potential for adverse systemic effects (Bulletti et al., 1997)
- The pregnancy rates after vaginal and i.m. progesterone support are comparable, despite higher serum levels after i.m. injection. Patients prefer the vaginal progesterone. (Penzias, 2002)

Patients Prefer vaginal over IM progesterone



Levine H., 2000

Oral progesterone

- Ineffective?
- Low bioavailability
- High rate of metabolites (scant endometrial effect)
- High rate of side effects (somnolence)

Oral progesterone ineffective?

- ✓ Progesterone administered orally is subjected to first-pass prehepatic and hepatic metabolism. This metabolic activity results in progesterone degradation to its 5 α - and 5 β -reduced metabolites. (Penzias, 2002)
- ✓ Bourgain (1990) and Devroey (1988) reported absence of any secretory transformation of the endometrium in patients treated with oral micronised progesterone compared to patients treated with intra muscular injections or vaginal micronised progesterone, suggesting a reduced bioavailability of this hormone, if taken orally.

Oral progesterone ineffective?

- ✓ Dydrogesterone (DG), a retroprogesterone with good oral bioavailability, is a biologically active metabolite of progesterone, which has an anti-estrogenic effect on the endometrium causing a secretory transformation (Whitehead, 1980)
- ✓ Chakravarty *et al.* (2005) in a prospective, randomised study compared the efficacy, safety and tolerability of vaginal micronised progesterone with oral dydrogesterone as luteal phase support after in-vitro fertilization (IVF). Both dydrogesterone (DG) and micronised progesterone (P) were associated with similar rates of successful pregnancies (24.1% vs. 22.8%, respectively; p=0.81).

Oral DG VS. Vaginal progesterone



Figure 1. Representative endometrial biopsy on day 21 of an artificial cycle after micronised progesterone. Patients with prominent secretory features received estradiol from days 1 to 21 and vaginal progesterone from days 13 to 21. Atypical glands with active secretion and increased vascularisation. Stained with hematoxylin. Magnification: 200x. The magnification corresponds to day-8 of the luteal phase characteristic and active staining. $\times 200$.



Figure 2. Representative endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and prominent homogeneous submucosal vascularisation and pseudostratified nuclei. (No uterine glands. Focal mitotic activity.) The magnification corresponds to days 2-5 of the luteal phase characteristic and active staining. $\times 200$.

Oral progesterone ineffective?

- ✓ A relatively retarded endometrial development in artificial cycles treated with oral dydrogesterone has been reported in several studies (Pellicer *et al.*, 1989; Li *et al.*, 1994, Fatemi *et al.*, 2007).
- ✓ The oral DG might be sufficient for luteal supplementation in IVF cycles, however; more large randomized controlled trails are needed, before a conclusion can be made.

hCG as a luteal support

- ✓ Progesterone and estradiol are hormone supplementations, whereas hCG is used to stimulate these hormones in the corpora lutea.
- ✓ Placental protein 14 (Anthony *et al.*, 1993), integrin αv (Honda *et al.*, 1997) and relaxin (lutel peptide hormone) concentrations, which has been shown to increase at the time of implantation are higher with hCG support (Ghosh and Sengupta, 1998)
- ✓ Limitations: OHSS. Luteal support with hCG should be avoided:
 - If E2 >2700pg/ml (Buvat *et al.*, 1990)
 - If Number of follicles is >10 (Araujo *et al.*, 1994)

hCG as a luteal support

Table 4. Meta-analysis of the relative risk and 95% CI of patients using HCG vs. progesterone

Study	HCG n/N	Progesterone n/N	OR (95% CI fixed)	Weight %	OR (95% CI fixed)
Albert and Pfeifer [11]	6/34	5/23		18.5	0.77 (0.20, 2.91)
Araujo <i>et al.</i> [7]	11/30	12/34		26.8	1.06 (0.38, 2.95)
Buvat <i>et al.</i> [10]	22/70	10/70		25.8	2.75 (1.19, 6.36)
Claman <i>et al.</i> [9]	13/72	7/49		25.7	1.32 (0.49, 3.60)
Golan <i>et al.</i> [8]	7/30	1/26		3.1	7.61 (0.87, 66.67)
Total (95% CI)	59/236	35/202		100.0	1.71 (1.06, 2.76)

Test for heterogeneity: $\chi^2 = 5.53$, d.f. = 4, $p = 0.24$.
 Test for overall effect: $z = 2.22$, $p = 0.03$.

Nosarka *et al.*,
2005

Is hCG in the luteal phase superior to i.m. progesterone?

- ✓ Pritts Meta analyse, 2002: six studies comparing i.m. hCG or i.m. progesterone were included. CPR were no different between groups (Albert and Pfeifer, 1991; Claman *et al.*, 1992; Araujo *et al.*, 1994; Artini *et al.*, 1995; Loh and Leong, 1996).
- ✓ In these studies, the long protocol of GnRH agonist treatment was used, and luteal support lasted as little as 2 weeks and for as long as 6 weeks gestation.

Is hCG in the luteal phase superior to vaginal progesterone?

- ✓ Intramuscular hCG was compared with vaginal progesterone in four data sets (Artini *et al.*, 1995; Martinez *et al.*, 2000; Ludwig *et al.*, 2001; Ugur *et al.*, 2001).
- ✓ In these studies, the long GnRH agonist protocol was used
- ✓ There were again no differences in CPR, OPR or SAB.

Is hCG in the luteal phase superior to progesterone at all?

- ✓ progesterone is as effective as hCG for luteal phase support but provides a higher safety with regard to ovarian hyper-stimulation syndrome (Ludwig and Diedrich, 2001)

Progesterone plus E2

- ✓ The role of progesterone for luteal support in stimulated cycles for IVF is well established. (Fatemi et al., 2006)
- ✓ However, controversy still surrounds the benefit of additional supplementation with estradiol (E2)
- ✓ Differences in agonist and antagonist cycles?

Progesterone plus E2:

- ✓ (Smitz et al., 1993): The clinical pregnancy rate was similar whether or not estradiol valerate was added to intravaginal progesterone by 378 infertile women in GnRH-agonist and HMG IVF cycles.
- ✓ Farhi et al. (2000), in a prospective, randomized study, evaluated the effect of adding E2 to progestin supplementation during the luteal phase in 271 patients undergoing IVF: It was shown that for patients who are treated with the long GnRH agonist protocol for controlled ovarian hyperstimulation (COH), the addition of E2 to the progestin support regimen has a beneficial effect on pregnancy and implantation rates.
- ✓ However, such an effect could not be shown in the short GnRH agonist protocol.

Progesterone plus E2:

- ✓ Lukaszuk et al. (2005), evaluated the effect of different E2 supplementation doses during the luteal phase on implantation and pregnancy rates in women undergoing ICSI in agonist cycles (n=231).
- ✓ Doses of 0, 2, or 6 mg of E2 during the entire luteal phase.
- ✓ Addition of a high dose of E2 to daily progesterone supplementation significantly improved the probability of pregnancy in women treated with a long GnRH analogue protocol for COH.

**Progesterone plus E2:
Differences in agonist and antagonist cycles?**

- ✓ Fatemi et al., 2006: 201 patients underwent COH with recombinant-FSH and GnRH-antagonist.
- ✓ Patients were randomised to receive, for luteal phase supplementation, either 600 mg of micronised progesterone vaginally (n=100, progesterone group) or 600 mg of micronised progesterone and 4mg of estradiol-valerate orally (n=101, progesterone/E2 group).

**Progesterone plus E2:
Differences in agonist and antagonist cycles?**

- ✓ 26% pregnancies were achieved in the progesterone and 29.7% in the progesterone/E2 group (Difference: 3.7%, 95% CI :-15.8% to 8.6%).
- ✓ It appears that the addition of E2 to progesterone in the luteal phase after stimulation with rec- FSH and GnRH antagonist does not enhance the probability of pregnancy.
- ✓ The difference in results, cannot be explained by the different forms of stimulation protocols used, since the luteal phase characteristics and dynamics of IVF cycles using GnRH agonist or antagonists have been shown to be similar (Friedler et al., 2006).

What is the best timing of Luteal support?

What is the best timing of Luteal support?

- ✓ The administration of progesterone before oocyte retrieval is associated with a lower pregnancy rate than the administration of progesterone after oocyte retrieval. (Sohn *et al.*, 1999)
- ✓ Decrease of 24% was seen when luteal phase support was delayed until 6 days after OR compared to 3 days after OR (Williams *et al.*, 2001)
- ✓ No difference was found when luteal phase support was started at OR compared to starting at ET (Baruffi *et al.*, 2003)

What is the best timing of Luteal support?

- ✓ Mochtar *et al.*, 2006, compared the effect of three different times of onset of luteal phase support on ongoing pregnancy rate in infertile patients undergoing treatment with GnRH down-regulated IVF and embryo transfer (IVF/ET)
 - Three groups, 385 women were randomized
 - HCG group
 - OR group
 - ET group (on day 3.)
 - luteal phase support until 18 days following OR
- ✓ An ongoing pregnancy rate of 20.8% was found in the HCG group versus 22.7 and 23.6% in the OR group and ET group, respectively

What is the best length of Luteal support?

- ✓ Does prolongation of luteal support during early pregnancy influences the delivery rate after IVF?
 - 200 mg vaginal progesterone three times daily during 14 days from the day of transfer until the day of a positive HCG test. The study group (n = 150) withdrew vaginal progesterone from the day of positive HCG. The control group (n = 153) continued administration of vaginal progesterone during the next 3 weeks of pregnancy. (Andersen *et al.*, 2002)

What is the best length of Luteal support?

Prolongation of progesterone supplementation in early pregnancy has **no** influence on the miscarriage rate, and thus no effect on the delivery rate.

Progesterone supplementation can safely be withdrawn at the time of a positive HCG test. (Andersen et al., 2002)

What is the best length of Luteal support?

▪First trimester progesterone supplementation in IVF may support early pregnancy through 7 weeks by delaying miscarriage but does not improve live birth rates.

▪Live birth rates (76.8% luteal protocol (2 weeks after retrieval) vs. 75.0% first trimester protocol; P=.80, n=172) (Proctor et al., 2006)

Does P reduce the miscarriage rate in pregnancies conceived in natural cycle ?

There is no evidence of effectiveness with the use vaginal progesterone compared to placebo in reducing the risk of miscarriage (relative risk 0.47; 95% confidence interval (CI) 0.17 to 1.30 (Wahabi et al., 2007- Cochrane Database Syst Rev.)

Conclusions

- prevalence of a luteal phase defect in natural cycles is about 8.1% (Rosenberg et al., 1980).
 - In these cases LPS is indicated
- CC/AI stimulated cycles seem not to disturb the luteal phase, however there is an urgent need for PRT.
- HMG/rec-FSH with GnRH agonist and antagonist cycles must be supplemented.

Conclusions

- **Luteal phase support with hCG or progesterone after assisted reproduction results in an increased pregnancy rate. (Cochrane, 2006, Daya and Gunby)**
- **HCG is associated with a greater risk of OHSS. Luteal support with hCG should be avoided:**
 - If E2 >2700pg/ml (Buvat et al., 1990)
 - If Number of follicles is >10 (Araujo et al., 1994)
- **Natural micronised progesterone is not efficient if taken orally (Bourgain 1990 and Devroey 1988)**

Conclusions

- The oral DG might be sufficient for luteal supplementation in IVF cycles, however; more large randomized controlled trails are needed, before a conclusion can be made.(Fatemi et al., in press. 2006)
- Vaginal and intra muscular progesterone seem to have comparable implantation and clinical PRs and DR (Nosarka et al.,2005)

Conclusions

- **LPS length:**

- 14 days from the day of transfer until the day of a positive HCG test. (Andersen et al., 2002)
- 18 days following OR (Mochtar et al., 2006)
- First trimester progesterone supplementation in IVF may support early pregnancy through 7 weeks by delaying miscarriage but does not improve live birth rates
- First trimester progesterone supplementation in natural cycle pregnancies also does not prevent a miscarriage. (Wahabi et al., 2007)
